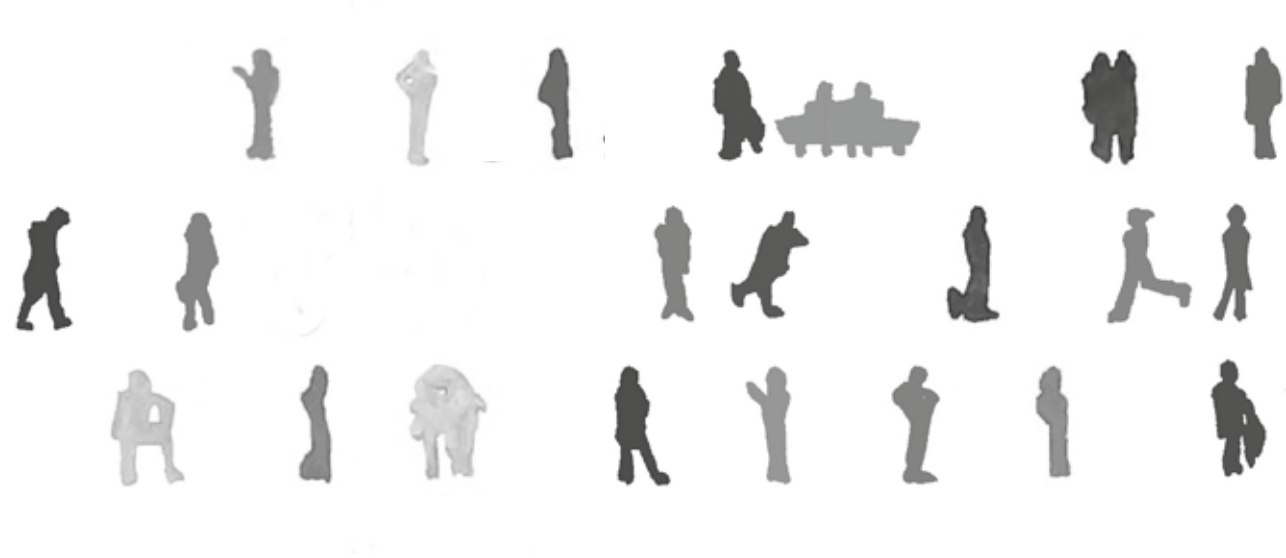
Chapter 7

Summary, general discussion and future perspectives



SUMMARY

In this thesis an option is presented to improve screening for and treatment of early stages of progressive kidney and cardiovascular disease (CVD). In a review (**chapter 2**) we described that atherosclerotic damage to the kidney is nowadays one of the most prevalent causes of chronic kidney disease (CKD). This frequently coincides with atherosclerotic damage to the heart, brain and lower extremities. As damage to the kidney is easy to measure by monitoring albuminuria and eGFR, and as the early phases of kidney damage frequently precede the alarming symptomatology of atherosclerotic disease in the heart, brain and peripheral vasculature, it is argued that the nephrologist should consider taking the lead in better organizing early detection and management of CKD and CVD. Only in case a subject is diagnosed in an early phase of CKD, which is the situation of elevated albuminuria and still relatively well-preserved kidney function, this subject can be treated early. Early start of treatment will generally also result in slowing the rate of progression of atherosclerotic CVD. Figure 1 demonstrates the potential benefit of early versus the traditional late intervention[1].

In **chapter 2** it is also emphasized that elevated albuminuria may not only be present in subjects with hypertension and/or diabetes, but that elevated albuminuria may also precede the development of hypertension and/or diabetes. These findings were the rationale for the studies described in the following chapters, which investigate whether screening for elevated albuminuria may improve cardiovascular (CV) and kidney care.

In the general population, many subjects with a CV risk factor are yet undiagnosed as having such a risk factor. Guidelines to prevent CVD argue for screening for those risk factors (such as hypertension and hypercholesterolaemia), based on case-finding. Subjects at risk for CVD (i.e. those with a history of CVD, diabetes, rheumatoid arthritis or CKD, a family history with CVD, known hypertension or hypercholesterolaemia, smoking or ≥50 years of age) should be screened when they visit their general practitioner for whatever cause, or they may be specifically called in for such a screening[2]. Such an approach is, however, labor and cost intensive. It is well known that elevated albuminuria is an early marker of vascular damage, associated with an increased CV risk and easy to measure. We studied in **chapter 3** in a random sample of the general, non-diabetic population, whether a pre-screening approach in which detailed risk factor measurement is done only after selection of subjects with elevated albuminuria results in a higher yield. It was found that the prevalence of undiagnosed CV risk factors (diabetes, hypertension, hypercholesterolaemia, impaired GFR and

elevated albuminuria) in the general population is considerably higher than the prevalence of known risk factors. After a pre-selection of subjects with elevated albuminuria, the relative prevalence of subjects with yet undiagnosed CV risk factors increases. Consequently the number of subjects to test for presence of CV risk factors is smaller.

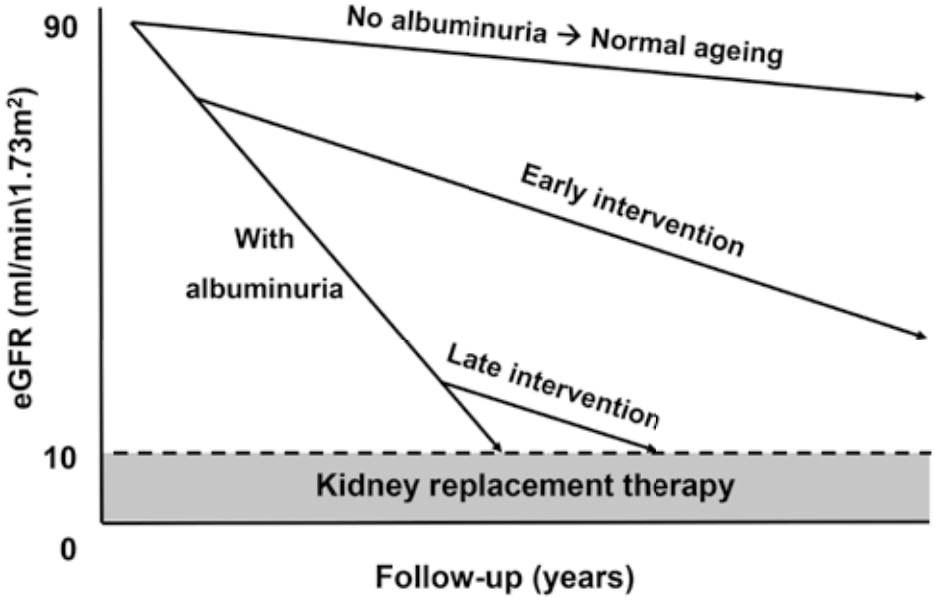


Figure 1. Schematic presentation of kidney function decline over the years and the effect of late versus early intervention to prevent the need for kidney replacement therapy. Adapted from Gansevoort et al.[1]

As mentioned above, many subjects in the general population have yet undiagnosed hypertension and hypercholesterolaemia, and are thus not treated. In **chapter 4** it was investigated whether population pre-screening for elevated albuminuria can identify subjects with previously undiagnosed hypertension and/or hypercholesterolaemia at high risk for CVD. In the group with, as well as in the group without elevated albuminuria, the number of subjects with yet undiagnosed hypertension and hypercholesterolaemia was at least 2-fold higher than the number of subjects known with these CV risk factors. The hazard ratio for CV events was significantly increased in the subjects with elevated albuminuria compared with those with normoalbuminuria, independent of whether they had

no CV risk factor present, a CV risk factor known or a CV risk factor newly discovered. The benefits of a pre-screening on albuminuria, followed by screening for hypertension or hypercholesterolaemia only when they have elevated albuminuria, instead of a screening first on hypertension or hypercholesterolaemia and second on albuminuria is evident: the 10 year CV event rate was 23.3 and 22.7% in case of elevated albuminuria with new diagnosed hypertension and hyper- cholesterolaemia, respectively, while it was 12.7 and 9.9% in subjects with newly diagnosed hypertension and hypercholesterolaemia in case they had no elevated albuminuria. In general, it is advised to start treatment for primary prevention of CVD in subjects with a 10-year CV risk above 20% and to consider starting such treatment when 10-year risk is between 10 and 20%[3-5]. Our data show that the CV event rate in those with elevated albuminuria crossed this recommended threshold to start antihypertensive or lipid-lowering treatment, not only when the CV risk factor was known, but also in the subgroup with a newly diagnosed CV risk factor. In subjects with a newly discovered CV risk factor without elevated albuminuria, absolute CV risk was significantly lower and also did not cross the recommended 10-year CV risk threshold of 20% for starting preventive treatment. Based on these data, we concluded that pre-screening for elevated albuminuria and subsequent screening for CV risk factors in those with elevated albuminuria identifies subjects with yet unknown CV risk factors at high risk for CV disease that are likely to benefit from early preventive treatment.

Next, in **chapter 5** we studied whether such a pre-screening strategy may also be of help to identify subjects at risk for accelerated decline in kidney function. For this study glomerular filtration rate (eGFR) was estimated with the CKD-EPI creatinine-cystatin C equation. Of the included 6471 subjects the decline in eGFR was greater in the subgroups with elevated albuminuria. This held true not only in albuminuric subjects with known hypertension, but also in subjects with newly diagnosed hypertension as well as in subjects with normal blood pressure. This effect was more pronounced in an older population, i.e. in subjects ≥55 years of age.

In addition, subjects with elevated albuminuria had higher blood pressure than subjects with normoalbuminuria, and in subjects with elevated albuminuria yet undiagnosed hypertension was twice as prevalent as diagnosed hypertension. From these data it can be concluded that pre-screening on albuminuria, followed by screening for hypertension only when they have elevated albuminuria, may be of help to detect subjects with increased risk for a steeper decline in kidney function, who may benefit from more strict antihypertensive treatment and especially from (a switch) to ACE inhibitors or Angiotensin-II receptor blockers.

Finally, we were interested in the role of elevated albuminuria as a tool to distinguish, which hypercholesterolaemic patients benefit most from statin treatment with respect to prevention of CV events. In **chapter 6** it was therefore studied in an observational cohort study whether subjects with hypercholesterolaemia benefit more from starting statin treatment when having elevated albuminuria and/or high-sensitivity C-reactive protein (hsCRP), both early signs of atherosclerotic vascular damage and tools to help identify CV high-risk patients. Our data indicate that the start of a statin was associated with a beneficial effect on CV event rate in subjects with elevated albuminuria, while the effect of starting a statin was less in subjects without elevated albuminuria. In contrast, the effect of starting a statin was similar in subgroups with high and low hsCRP. When combining albuminuria and hsCRP subgroups, the start of statin treatment was associated with a lower risk of CV events dependent on albuminuria status and not on hsCRP level. It was concluded that the start of statin treatment is associated with a significantly better absolute as well as relative risk reduction in CV event rate in subjects with hypercholesterolaemia and elevated albuminuria, whereas such treatment had less effect in subjects with normal albuminuria.

GENERAL DISCUSSION

The definition of screening, and the criteria to appraise the validity of a screening program, were referred to in the introduction of this thesis. A detailed discussion whether population screening for albuminuria fulfills all these criteria is beyond the scope of this thesis. Such a discussion has been provided in an earlier publication of our group[6]. In this thesis specifically two criteria were addressed, first, "what is the defined target population" and, second, "whom should we treat as patients?"

With respect to the question what the target population to screen is, it was argued in **chapter 5** that it is more appropriate to screen the population above the age of 55 years for elevated albuminuria, because in such persons the prevalence of elevated albuminuria is higher, as well is absolute risk for progressive CVD and CKD. Pre-screening for albuminuria in these subjects could be organized by asking them to collect at home a portion of an early morning urine void in a test tube, and sending this tube by post to a central laboratory for albuminuria measurement. Subsequently, only those who have elevated albuminuria are invited to collect a second urine sample. In case elevated albuminuria is confirmed, these subjects could be invited to a screening facility or to their general practitioner for a blood test on glucose and lipid levels, and for blood pressure measurement.

By choosing for this approach, the costs of the pre-screening are just limited to sending an invitation to everyone in this age category, and measuring urinary albumin in those who send back their test tube. The more elaborate and costly procedures of measuring blood pressure and collecting a blood sample for measurement of lipids, glucose and eGFR, is limited to the subjects who are positive for albuminuria (which probably will be the case in 10-20% of the population, depending on the age of the cohort and the albuminuria threshold that is chosen to indicate elevated albuminuria). This approach will probably be more cost effective than the aforementioned present case-finding screening approach, in which the same age cohort is screened first on blood pressure, cholesterol and glucose, and subsequently measuring albuminuria and eGFR in those who are hypertensive, diabetic or hypercholesterolaemic.

With respect to the question whom we should treat, we argue that those in whom elevated albuminuria is confirmed should be considered for treatment to reduce the incidence of CKD and/or CVD. The international KDIGO guideline for management of CKD advises that both diabetics and non-diabetics with an albuminuria ≥30 mg/day should be treated with an ACE inhibitor or an angiotensin

II receptor blocker in case of a blood pressure >130/80 mmHg, whereas those with an albuminuria equal to or ≥300 mg/day even should receive such an agent independent of blood pressure[7]. There is no consensus yet in guidelines whether subjects with an albuminuria ≥30 mg/day and a blood pressure <130/80 mm Hg should be treated with these agents.

The drawback of a pre-screening approach in which only subjects are screened for presence of CV risk factors in case they have elevated albuminuria is of course that subjects without elevated albuminuria and yet undiagnosed hypertension and/or hyper-cholesterolaemia are not detected, and thus will not receive treatment for hypertension or hypercholesterolaemia. As shown in **chapter 4**, the newly diagnosed hypertensive subjects without elevated albuminuria have a CV event rate that, though higher than in non-hypertensive subjects, is no more than 12.7% per 10 year. That event rate is below the threshold of 20% at which treatment should be started, and equal to the event rate in subjects with elevated albuminuria but without hypertension, for which, as mentioned above, treatment is generally not advised in prevailing guidelines.

In **chapter 5** we suggested to combine our albuminuria based pre-screening approach to detect subjects at high-risk for progressive CVD and CKD with the existing screening program for colorectal cancer. In several Western-European countries the population aged >55 years is nowadays invited to send a vial containing a feces sample by post to a central laboratory for testing for occult blood loss. Those who have a positive feces occult blood test are invited for follow-up measurements, such as coloscopy. This screening program could easily be extended by additionally asking subjects to collect an early morning urine void in a test tube, and to add this tube to the package to be returned by post to the central screening laboratory.

Colorectal screening is repeated every 2 years till the age of 75 years. Brantsma et al suggested, based on results of the PREVEND study, to repeat screening for elevated albuminuria once every 4 years in subjects who tested initially negative[8]. Because CKD in general is a slowly progressive disease, albuminuria retesting after a period of 4 years could be sufficient to allow timely detection of elevated albuminuria. An additional and an important objective of this screening method is to detect also subjects with high-risk for CVD. It has been calculated that in case this objective is taken into account, screening the general population aged >50 and >60 years for albuminuria meets the requirements for cost-effectiveness when repeat screening takes place each ≥3 years[9]

In our opinion the age threshold of 75 years above which repeat colorectal cancer screening is stopped could also be used for albuminuria screening, be-

cause if a solitary elevated albuminuria was detected in a subject of 75 years or older, the absolute health gain with respect to prevention of progressive CVD and CKD will probably be limited.

Limitations of screening and early detection of high-risk subjects include the psychological effects of being labeled with a diagnosis of CKD and/or CVD. Moreover, there is limited accuracy in predicting prognosis for any given individual, at least when the Framingham risk score or the SCORE 10 year CV risk calculator are used, as advocated in current CardioVascular Risk Management guidelines[2,10,11]. However, adding eGFR and albuminuria to the variables included in these risk calculators may improve the risk prediction. As for every screening program, a false-positive test could lead to unnecessary concern, tests and financial and insurance ramifications. For this reason we propose that elevated albuminuria at the initial screening should be confirmed by a second test before subjects are invited for elaborated screening for CV risk factors. In addition, false-negative tests can theoretically also give false reassurance and inadvertently lead to unhealthy behavior. Whether this is a real concern has to our knowledge not been investigated.

Based on the data obtained in the various studies described in this thesis, that indicate an important role of elevated albuminuria for CVD and CKD risk prediction, a role for the nephrologist is suggested in guiding the general practitioner and health care workers to offer better preventive care. For instance, it is necessary to take a more active role in developing guidelines, education and further cooperation with general practitioners on a national as well as local level. Above all, it is important that nephrologists take the responsibility to increase awareness among the general population and among physicians of the importance of early stages of CKD to determine risk for incident end-stage kidney and CV disease. In this way the nephrologist can contribute to minimize not only the need for renal replacement therapy, but also to prevent CV disease.

The studies in this thesis and those from literature suggest that cardiovascular risk management by the general practitioner should be modified. First, in the summary of risk factors not only an impaired eGFR, but also an elevated albuminuria should be mentioned. At present albuminuria has a limited place as cardiovascular risk marker. Only in subjects with diabetes mellitus it is acknowledged as risk marker.[12] However, recent data has convincingly shown that the association of albuminuria with cardiovascular risk is not different between subjects with and without diabetes mellitus.[13] Second, it has become clear that patients with CKD, defined by either impaired eGFR or increased albuminuria, are at especially high-risk for cardiovascular events.[14-16] Consequently, it seems

prudent that in CKD patients with other risk factors for CVD, a more aggressive treatment of these risk factors should be instituted like that is advocated for patients with prior CV events, diabetes and/or with rheumatoid arthritis. The recent SPRINT study, as well as two meta-analyses, indicate that in such patients strict blood pressure control will result in less cardiovascular events and even all cause mortality.[17-19] The blood pressure target in patients with CKD defined as elevated albuminuria should therefore be <130/80 mmHg. Another aspect that in our opinion should be adapted is the approach in the present 'Het Preventie-Consult'.[20] Thus far eGFR and albumin-to-creatinine ratio are only measured after hypertension or hypercholesterolaemia is confirmed. We argue that these two parameters that define CKD, should be measured direct at the beginning, thus in the same session where blood glucose and plasma lipids are measured, especially in subjects ≥55 years of age.

FUTURE PERSPECTIVES

In 2006 the Dutch Kidney Foundation started an awareness campaign called 'Stop beginning kidney disease'. Citizens were encouraged to order a "kidney check", that is a dipstick urine test for albuminuria at home. Surprisingly, nearly 1.6 million of all adult Dutch citizens asked for this "Kidney Check"[21]. The Dutch colorectal cancer screening program also seems to be very successful with a participation rate of about 68% of the invited population[22]. These high participation rates indicate that the Dutch population accepts screening programs.

Based upon the data in this thesis, we propose to combine the fecal blood test screening via post for all subjects aged 55-75 years with a urinary albumin test. The subjects with elevated albuminuria will be sent a second urine test for confirmation. When elevated albuminuria is confirmed, these subjects should be offered a further screening program including screening for established CV and kidney risk factors. This could take place in a screening facility or in cooperation with their own general practitioner. Based on the data that will be collected, a personal risk prediction can be carried out, leading to a 'tailor made' treatment advice.

If the presently available evidence, that such a urinary albumin testing screening will improve health outcomes with respect to CVD and CKD and its cost-effectiveness, does not yet convince one it might be a next step to carry out a formal implementation study. This could either be a simple study, that just investigates participation rate in pre-screening the general population aged 55-75 years, or a more elaborate study as indicated in Figure 2. In the latter study subjects in the age group of 55-75 years are randomized to either of two groups. One group is a control group (group A), in which no screening or intervention will take place, but that will only be monitored for the incidence of (non-) fatal CV events and end-stage kidney disease and health care utilization. The other group (group B) is sent an invitation to participate in an evaluation whether health outcomes will be improved when they are screened for albuminuria (the pre-screening sent by post). With the invitation to participate, they are sent a questionnaire on general health status, with emphasis on CV and kidney disease and two test tubes, which they have to return by post to a central laboratory with a first morning urine sample (the pre-screening). The second tube is necessary for confirmation of elevated albuminuria.

Subjects with an albumin-to-creatinine ratio (ACR) of ≤3.0 mg/mmol will undergo no further testing (group B1). In case ACR is confirmed to be >3.0 mg/mmol (the definition for elevated albuminuria in the international KDIGO guideline for classification of CKD) subjects are invited for the more elaborated screening in-

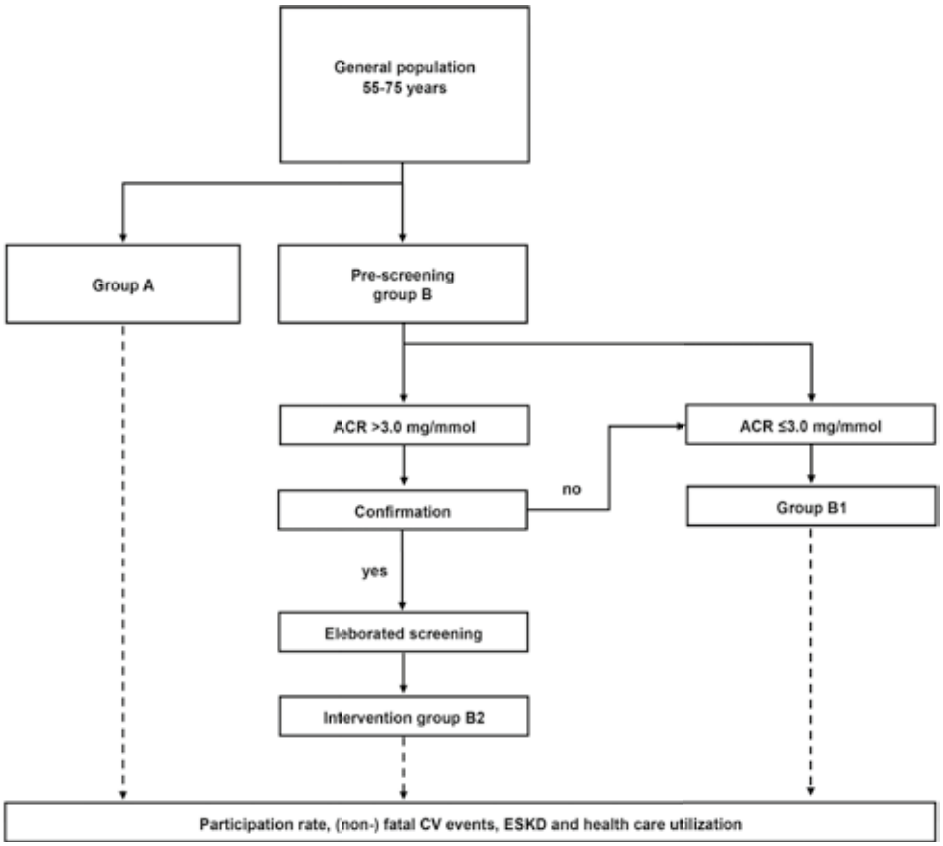


Figure 2. Schematic presentation of the formal implementation study for albumin screening.

Abbreviations: ACR= albumin-to-creatinine ratio, CV=cardiovascular, ESKD=end-stage kidney disease.

cluding blood pressure measurements and blood testing for glucose, cholesterol and eGFR (the actual intervention group, group B2)[7]. The general practitioners of the subjects in this group with an elevated ACR will receive the advice to treat their patients according to the recently updated guideline on the Diagnosis and Treatment of Patients with Chronic Kidney Disease of the Dutch Society of Nephrology and according to the guideline CardioVascular Risk Management[2,23].

Outcomes of this implementation study are, first, to investigate willingness to participate (i.e. the participation rate), and, second, to evaluate the effect of albuminuria screening approach on survival and on cardiovascular and kidney endpoints. These latter data will be collected via the Central Bureau of Statistics and the Dutch Hospital Data system. This study will have to be combined with

a cost-effectiveness analysis. When the outcome of the study is positive, i.e. sufficient participation, a positive effect on health outcomes and an acceptable cost-effectiveness ratio, albuminuria screening could be implemented, preferably as was argued before, in combination with colorectal cancer screening.

Even when a population albuminuria screening program would not yet be accepted, the data described in this thesis could have consequences. For instance, in order to decide which subjects are to be treated for CV risk management individualized risk prediction is needed. To that purpose risk calculators have been developed, such as the Framingham risk score and the SCORE cardiovascular risk calculator[10,11], but these risk calculators are not yet optimal, especially in subjects with CKD[24]. Moreover, these risk calculators do not incorporate eGFR and/or albuminuria for individualized risk prediction. As shown in **chapters 4** and **5** information on albuminuria can be of help to predict risk for CVD and CKD progression. The Chronic Kidney Disease Prognosis Consortium has further developed this notion in a recent study[14]. Matsushita et al. incorporated in a meta-analysis individual-level data of more than 600,000 individuals without a history of CVD from 24 observational cohorts. These authors showed that the addition of eGFR and ACR significantly improved the discrimination of CV outcomes beyond traditional risk factors in general populations during a 5-year time frame. The improvement was greater with ACR than with eGFR, and most evident for CV mortality and heart failure. The discrimination improvement with eGFR or ACR was especially evident in individuals with diabetes or hypertension, but remained significant with ACR for CV mortality and heart failure in those without either of these disorders. In individuals with CKD, the combination of eGFR and ACR for risk discrimination outperformed most single traditional predictors. The authors therefore concluded that creatinine-based eGFR and albuminuria should be taken into account for CV risk prediction. Especially in populations with CKD, the simultaneous assessment of eGFR and ACR could facilitate improved classification of CV risk, supporting current guidelines for CKD. These results also lend support to incorporate eGFR and ACR into assessment of CV risk in subjects of the general population.

Taken together, the studies that are described in this thesis lead to the conclusion that it is possible to use albuminuria as pre-screening tool for a better risk prediction for progressive CVD and CKD. Subjects with elevated albuminuria should be screened for presence of established CV risk factors and impaired eGFR, which have a relatively high prevalence in this population. Those with known or newly diagnosed risk factors are at high-risk for progressive CV and kidney disease, them may benefit from preventive treatment, to be intensified or started according to prevailing guidelines.

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